Alcam Regulates Long-term Hematopoietic Stem Cell Engraftment and Self-Renewal.

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Public Summary:

Scientific Abstract:
Hematopoietic stem cells (HSCs) reside in a specialized bone marrow (BM) microenvironment that supports the maintenance and functional integrity of long-term (LT)-HSCs throughout postnatal life. The objective of this work is to study the role of activated leukocyte cell adhesion molecule (Alcam) in HSC differentiation and self-renewal using an Alcam-null (Alcam(-/-)) mouse model. We show here that Alcam is differentially regulated in adult hematopoiesis and is highly expressed in LT-HSCs where its level progressively increases with age. Young adult Alcam(-/-) mice had normal homeostatic hematopoiesis, and normal numbers of phenotypic HSCs. However, Alcam(-/-) HSCs had reduced long-term replating capacity in vitro and reduced long-term engraftment potential upon transplantation. We show that Alcam(-/-) BM contain a markedly lower frequency of long-term repopulating cells than wild type (WT). Further, the long-term repopulating potential and engraftment efficiency of Alcam(-/-) LT-HSCs was greatly compromised despite a progressive increase in phenotypic LT-HSC numbers during long-term serial transplantation. In addition, an age-associated increase in phenotypic LT-HSC cellularity was observed in Alcam(-/-) mice. This increase was predominately within the CD150(hi) fraction, and was accompanied by significantly reduced leukocyte output. Consistent with an aging-like phenotype, older Alcam(-/-) LT-HSCs display myeloid-biased repopulation activity upon transplantation. Finally, Alcam(-/-) LT-HSCs display premature elevation of age-associated gene expression, including Selp, Clu, Cdc42, and Foxo3. Together, this study indicates that Alcam regulates functional integrity and self-renewal of LT-HSCs.